These amendments are made without prejudice and are not to be construed as abandonment of the previously claimed subject matter or agreement with the Examiner's position. In accordance with the requirements of 37 C.F.R. § 1.121, a marked up version of the claims showing the changes, is attached as Appendix A. For the Examiner's convenience, a complete set of the currently pending claims is also provided as Appendix B.

REMARKS

Status of the Claims.

Claims 56-59 and 64-68 and 70-80 are pending with entry of this amendment, claims 60-63 and 69 being cancelled without prejudice. Claims 56, 64, 68, 70, 71, and 76 are amended herein. Support for the amendments is found generally throughout the specification; see, for example, page 29, line 13 to page 34, line 26. These amendments therefore introduce no new matter.

Election/Restriction.

Pursuant to a restriction requirement made final, Applicants cancel claims 60-63 with entry of this amendment. Please note, however, that Applicants reserve the right to file subsequent applications claiming the canceled subject matter and that the claim cancellations should not be construed as abandonment or agreement with the Examiner's position in the Office Action.

35 U.S.C. § 112, First Paragraph.

Claims 56-59 and 64-80 were rejected under 35 U.S.C. § 112, first paragraph, on the ground that that the specification does not enable one skilled in the art to practice the claimed invention. Office Action, page 2. This rejection is respectfully traversed.

The Examiner bases the rejection on two different rationales. First, the Examiner asserts: "A step of comparing the binding of the test agent to or activity of PKC epsilon with other PKC isozymes is critical or essential to the practice of the invention, but not included in the claims(s)." *Id.* Applicants respectfully submit that such a step is, in fact, not necessary to practice the invention recited in the pending claims, except for claim 70. As discussed in detail below, claim 70 inherently incorporates such a comparison.

The second rationale for the rejection is that allegedly "the specification, while being enabling for practicing the claimed methods wherein an agent is screened for specifically binding to

PKC epsilon and specifically inhibiting the activity of PKC epsilon, does not reasonably provide enablement for other embodiments, for example, wherein the modulator is an activator of PKC epsilon activity." Office Action, page 3. Claims 64-68 and 70-80 relate either to screening by "determining whether the test agent inhibits PKCε" (claims 64-68 and 70-75) or "selecting an agent that inhibits PKCε as a test agent" (claims 76-80). Applicants therefore submit that this aspect of the rejection is moot as to these claims. The remaining claims (claims 56-59) relate to screening test agents for binding to PKCε. As discussed further below, Applicants submit that the specification fully enables these claims.

Turning to the first rationale for the § 112, first paragraph rejection, the Examiner states that the "claimed invention is based on the finding of the inventors that a null mutation in PKC epsilon causing complete loss of PKC epsilon activity results in less anxiety related symptoms in a transgenic mouse." *Id.* The Examiner notes that "an inhibitor or activator that binds to one isozyme of PKC will also bind and inhibit or activate other isoforms of PKC." *Id.* Applicants agree that this will be true for some, but not all, agents that bind PKCε. That is, some agents will bind and/or inhibit or activate PKCε selectively and some will not.

The examiner notes that "all the examples described in the specification are based on the comparison of all the results in [a] PKC epsilon null mouse with those normal wild type mouse, which clearly indicates the essentiality of the use of a control in practicing the claimed invention." Office Action, pages 2-3. Applicants respectfully disagree with this statement. The use of a control mouse was important to observe the effect of eliminating PKCε on anxiety. In other words, to establish that a reduction in PKCε correlated with a reduction in anxiety, studies comparing anxiety symptoms in animals lacking PKCε with anxiety symptoms in animals having normal PKCε levels were carried out. However, the use of wild-type control animals in studies that demonstrate a role for PKCε in modulation of anxiety says nothing about how methods based on this discovery should be carried out. The Examiner indicates that because the studies described in the specification included a comparison with wild-type control mice, the claimed methods must specifically recite a comparison with a particular control. This line of reasoning overlooks the fact that the claims relate to methods of screening for an agent that modulates anxiety, not to a method of demonstrating that PKCε has a role in modulating for anxiety. The Examiner is, in effect, "comparing apples and

oranges" in an effort to show that the specification establishes the "essentiality of the use of [a] control in practicing the claimed invention." Office Action, page 4.

It may be helpful at this point to consider the actual language of the claimed methods. The pending claims include three independent claims, namely claims 56, 64, and 76. Claim 56 recites:

> A method of screening for an agent that modulates anxiety, said method comprising:
>
> a) exposing a PKCε to a test agent;
>
> b) assaying for binding of the test agent to the PKCε; and
>
> c) if binding is detected, selecting the test agent as a potential modulator of anxiety.

The point of this method is to identify test agents capable of binding PKCε, because such agents are candidate modulators of PKCε, and thus potential modulators of anxiety. This method is complete when the test agent is either (i) determined not to bind PKCε or (ii) binds PKCε and is selected as a potential modulator of anxiety.

The Examiner is concerned that the "use of a control PKC epsilon isozyme to differentiate between the effects of modulator on PKC epsilon or any other isozyme will be crucial to practicing the claimed invention." Office Action, page 3. This concern is misplaced. The Examiner believes that the test agent must be determined to bind PKCε selectively, but selective binding is not a requirement of the method. The method simply identifies test agents that bind PKCε and selects them as potential modulators of anxiety. Agents that bind PKCε are potential modulators of anxiety because they may, for example, inhibit PKCε, and thereby reduce anxiety *in vivo*. Test agents selected in the method may or may not be selective for PKCε over other PKC isozymes. Although PKCε-selective agents may, in some cases, be preferred, both selective and non-selective agents that modulate PKCε can reasonably be expected to modulate anxiety in light of Applicants' demonstration that PKCε plays a role in anxiety. Because the determination of PKC isozyme selectivity is not an element of the method recited in claim 56, there is no reason that this claim should recite a step of comparing test agent binding to PKCε with test agent binding to another PKC isozyme. Applicants note that the same is true of claims 57-59, which depend from claim 56.

Claim 64 recites:

A method of screening for an agent that modulates anxiety, said method comprising:

a) exposing a functional PKCε, or a cell or cell lysate comprising a functional PKCε, to a test agent;

b) determining whether the test agent inhibits PKCε; and

c) if the test agent inhibits PKCε, selecting the test agent as a potential modulator of anxiety.

The point of this method is to identify test agents capable of inhibiting PKCε, because such agents are potential modulators of anxiety. This method is complete when the test agent is either (i) determined not to inhibit PKCε or (ii) inhibits PKCε and is selected as a potential modulator of anxiety.

The Examiner believes that the "use of a control PKC epsilon isozyme to differentiate between the effects of modulator on PKC epsilon or any other isozyme will be crucial to practicing the claimed invention." Office Action, page 3. As with claim 56, the method recited in claim 64 does not require a determination that test agent selectively inhibits PKCε. The method simply identifies test agents that inhibit PKCε and selects them as potential modulators of anxiety. Test agents selected in the method may or may not be selective for PKCε over other PKC isozymes. Although PKCε-selective agents may, in some cases, be preferred, both selective and non-selective agents that inhibit PKCε can reasonably be expected to modulate anxiety in light of Applicants' demonstration that PKCε plays a role in anxiety. There is simply no basis in claim 64 or in the specification for requiring Applicants' claims to rule out test agents that bind or inhibit other PKC isozymes, in addition to PKCε. Accordingly, there is no reason that claim 64 should recite a step of comparing test agent effects on PKCε with test agent effects on another PKC isozyme. The same is true of claims 65-68 and 71-75, which depend from claim 64.

Applicants note the Examiner's statement that "if a general PKC substrate was [*sic*] used, an artisan would not know if the change in enzyme activity was due to PKC epsilon or PKC gamma or any other isozyme." Office Action, pages 4-5. Applicants agree, but point out that independent claim 64 (to which this statement seems most relevant) recites " determining whether the test agent inhibits PKCε." This step requires that the assay be carried out under conditions such that any inhibition observed must be attributable to inhibition of PKCε, and not to inhibition of

another isozyme. Thus, the situation that the Examiner proposes, namely an assay using a non-specific substrate where multiple PKC isozymes are present would not be selected by the one skilled in the art for carrying out the claimed method. In other words, the Examiner's proposed assay would not meet claim 64's requirement for " determining whether the test agent inhibits PKCε." Thus, this proposed assay is outside the scope of claim 64.

Claim 70 depends from claim 64 and recites:

> The screening method of claim 64 wherein determining whether the test agent inhibits PKCε comprises measuring the ability of the test agent to selectively inhibit PKCε activity.

As one skilled in the art would readily appreciate, "measuring the ability of the test agent to selectively inhibit PKCε activity" inherently requires comparing the ability of the test agent to inhibit PKCε activity with its ability to inhibit the activity of another PKC isozyme. Accordingly, claim 70 recites a method that ***does*** require a determination that test agent selectively inhibits PKCε and, appropriately, recites "measuring" this ability. Applicants submit that such measuring inherently incorporates the "use of a control PKC isozyme to differentiate between the effects of modulator of PKC epsilon" and the effects on the "control" isozyme. Claim 70 is therefore clearly free of this rejection.

Claim 76 recites:

> A method of screening for an agent that modulates anxiety, said method comprising:
>
> a) selecting an agent that inhibits PKCε as a test agent;
>
> b) administering the test agent to an animal; and
>
> c) measuring one or more indicators of anxiety to determine whether the test agent modulates anxiety in the animal.

Claim 76 contains no requirement that the recited test agent inhibit PKCε selectively, nor is any such requirement found in dependent claims 76-80. Accordingly, the "use of a control PKC isozyme to differentiate between the effects of modulator on PKC epsilon or any other isozyme" is irrelevant to these claims.

The second rationale for the § 112, first paragraph rejection is that, according to the Examiner, "the specification, while being enabling for practicing the claimed methods wherein an agent is screened for specifically binding to PKC epsilon and specifically inhibiting the activity of

PKC epsilon, does not reasonably provide enablement for other embodiments." Office Action, page 3. Applicants believe that this rejection now applies only to claims 56-59, as the remaining pending claims ***are*** drawn to screening for or selecting test agents that inhibit PKCε.

In explaining the rejection, the Examiner states: "It is noted that the claimed invention would include screening for agents that bind to and activate PKC epsilon, however, the specification does not teach . . . how an artisan [would] use an activator of PKC epsilon as intended." Office Action, page 4.

As discussed above, claims 56-59 relate to a " method of screening for an agent that modulates anxiety," wherein test agents are screened based on their ability to bind PKCε. Any test agent that binds is selected as a potential modulator of anxiety. As is standard in drug development, subsequent assays can be carried out to determine whether the test agent has the ability to modulate anxiety as desired. That one or more subsequent assays will generally be carried out on any test agent selected for PKCε binding does not negate the utility of the claimed assay as a means of identifying potential modulators of anxiety that should be selected for further study. More specifically, the claimed method allows the researcher to screen a large number of test agents and to focus in on those test agents that may modulate PKCε activity by binding directly to the enzyme. That some of these test agents may activate PKCε is irrelevant because, if such agents are not of interest, they can be eliminated in a subsequent screen for effect of the test agent on PKCε activity. Applicant emphasize that any such subsequent screen is not part of the claimed method, which is complete when a test agent is either (i) determined not to bind PKCε or (ii) binds PKCε and is selected as a potential modulator of anxiety. If the Examiner believes that claim 56 should be amended to clarify that this claim recites a method that will generally be a preliminary screen in a larger drug development effort, Applicants would be willing to amend claim 56 to recite, for example, a "***prescreening*** method."

Applicants note that the Examiner does not contend that the specification fails to enable one skilled in the art to carry out a PKCε binding assay such as that recited in claims 56-59. As the specification need enable only that which is claimed, Applicants submit that the specification fully enables claims 56-59.

Withdrawal of the § 112, first paragraph rejection is respectfully requested.

35 U.S.C. § 112, Second Paragraph.

Claims 56-59 and 64-80 were also rejected under 35 U.S.C. § 112, second paragraph as allegedly "incomplete for omitting essential steps, such omission amounting to a gap between the steps." Office Action, page 5. According to the Examiner," the omitted steps are: determining the specificity of the binding to PKC epsilon and determining the specificity of the modulation of PKC epsilon by comparing with other PKC isozymes." *Id.*

As explained above, the comparison cited by the Examiner is ***not*** essential to the inventions recited in claims 56-59, 65-69, and 71-80. The only pending claim for which this comparison need be carried out is claim 70. However, claim 70 requires " measuring the ability of the test agent to selectively inhibit PKCε activity" and therefore inherently incorporates the comparison of test agent effect on PKCε with test agent effect on another PKC isozyme.

As the pending claims do not omit any essential steps, Applicants respectfully request withdrawal of the § 112, second paragraph rejection.

35 U.S.C. § 102.

Hundle et al.

Claims 56-59 and 64-70 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Hundle *et al.* (Journal of Biological Chemistry (1995) 270:30134-30140). This rejection is respectfully traversed.

In explaining the rejection, the Examiner stated:

> [W]hile the cited art does not explicitly teaches [*sic*] a method for screening of an agent that modulates anxiety, the recited method . . . has only two steps, exposing the PKC epsilon to a test agent and detecting binding and both these steps are taught by the cited reference. It is further noted that since the relationship of ethanol and anxiety were well known in the art at the time of the invention, a compound that alters PKC epsilon will have anxiety modulating activity.

Office Action, page 6.

To establish a *prima facie* case of anticipation, the Examiner must show that each element of the claimed invention is found, expressly or under principles of inherency, in a single cited reference. See *Diversitech Corp. v. Century Step, Inc.*, 7 U.S.P.Q. 2d 1315, 1317 (Fed. Cir. 1988).

As amended, independent claims 56 and 64 both recite a third step. Specifically, claim 56, which is drawn to screening test agents based on PKCε binding, recites: "if binding is detected, selecting the test agent as a potential modulator of anxiety." Claim 64, which is drawn to screening test agents based on inhibition of PKCε, recites: "if the test agent inhibits PKCε, selecting the test agent as a potential modulator of anxiety." Thus, both of the rejected independent claims incorporate an active step that is based on the Applicants' demonstration that PKCε plays a role in anxiety. In the absence of the teachings of Applicants' specification, one skilled in the art would not carry out these steps.

With regard to the Examiner's contention that "the relationship of ethanol and anxiety were well known in the art at the time of the invention," Applicants note that the Office Action fails to indicate exactly what this well-known relationship is. If the Examiner maintains this contention, Applicants respectfully request that the Examiner cite a reference establishing the nature of this relationship and that it was well known before the priority date of the present application or provide an Examiner's Affidavit establishing these points based on the Examiner's personal knowledge.

The Examiner observes that the Hundle reference teaches the "effect of ethanol . . . on PKC epsilon activity and expression." *Id.* This teaching, combined with the so-called "well known relationship" between ethanol and anxiety leads the Examiner to conclude that one skilled in the art would have known, before the present application's priority date, that "a compound that alters PKC epsilon will have anxiety modulating activity." *Id.* This line of reasoning does not withstand scrutiny. Hundle teaches that, in PC-12 cells, "ethanol increases the levels of . . . ε-PKC." Hundle, abstract. The record is devoid of any clear rationale as to how a teaching that ethanol increases the levels of PKCε in PC-12 cells would lead one skilled in the art to screen for and select test agents that bind to or inhibit PKCε as potential modulators of anxiety. Thus, the record fails to establish that Hundle teaches or suggest all of the elements of independent claims 56 and 64.

The only teaching of a link between PKCε and anxiety is in Applicants' specification. Moreover, Applicants' have demonstrated that PKCε "knockout" mice are less anxious than wild-type mice, establishing a correlation between ***reduced*** PKCε and ***reduced*** anxiety. Applicants submit that, if Hundle's teaching that ethanol ***increases*** PKCε has any relevance to Applicants' discovery, such relevance is not clear from this record.

Because Hundle fails to teach or suggest every element of the invention recited in independent claims 56 and 64, Hundle also necessarily fails to teach or suggest every element recited in the corresponding dependent claims (claims 57-59, 64-68, and 70-75). Accordingly, Hundle does not anticipate any of the pending claims. Withdrawal of the § 102 rejection over Hundle is therefore respectfully requested.

Mochly-Rosen et al.

Claims 56, 58, 64, 66, 69, and 70 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by a U.S. patent issued to Mochly-Rosen *et al.* Office Action, page 6. The Office Action identifies this patent as "US 7,783,405, 7-21-02, effective filing date 2-1-1994;" however, no such patent exists. As the Examiner did not list this patent on the Notice of References Cited (Form PTO-892), Applicants believe that the Examiner intended the rejection over U.S.P.N. 5,783,405, which issued July 21, 1998, has an effective filing date of February 1, 1994, and is listed on Applicants' Information Disclosure Statement. This rejection is addressed with regard to this patent and is respectfully traversed.

The Examiner states that the Mochly-Rosen patent "teaches inhibition of PKC epsilon activity by different inhibitors, such as PCK [*sic*] epsilon fragments, different chemical inhibitors of PKC epsilon such as PMA." *Id.* For the record, Applicants note that PMA stimulates, rather than inhibits, PKC isozymes. The Examiner acknowledges that "the cited patent does not teach that PKC epsilon inhibitors have potential anxiety modulation activity." *Id.* However, as for the § 102 rejection over Hundle, the Examiner nevertheless rejects the claims because "the recited method . . . has only two steps, exposing the PKC epsilon to a test agent and detecting binding." *Id.*

Of the rejected claims, only 56 and 64 are independent, and these claims have been amended to incorporate a third step. Specifically, claim 56 recites: "if binding [of a test agent to PKCε] is detected, selecting the test agent as a potential modulator of anxiety." Claim 64 recites: "if the test agent inhibits PKCε, selecting the test agent as a potential modulator of anxiety." Thus, both of the rejected independent claims incorporate an active step that is based on the Applicants' demonstration that PKCε plays a role in anxiety. In the absence of the teachings of Applicants' specification, one skilled in the art would not carry out these steps.

Because Mochly-Rosen fails to teach or suggest every element of the invention recited in independent claims 56 and 64, Hundle also necessarily fails to teach or suggest every

element recited in the rejected claims depending from claims 56 and 64 (claims 58, 66, 69, and 70). Accordingly, Mochly-Rosen does not anticipate any of the pending claims. Withdrawal of the § 102 rejection over this reference is therefore respectfully requested.

Onaivi et al.

Claims 56-59 and 64-80 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Onaivi *et al.* (Annals of NY Acad. Of Sci. (1998) 844:227-244) Office Action, page 7. The rejection is respectfully traversed.

Among the various rationales that the Examiner gives for this rejection is the one underlying each of the other § 102 rejections, namely: "although the art does not explicitly teach an in vitro method for screening of an agent that modulates anxiety, the recited method . . . has only two steps, exposing the PKC epsilon to a test agent and detecting binding[,] and both of these steps are taught by the cited reference." *Id.* Applicants disagree with this conclusion, but note that, in any case, independent claims 56 and 64 now recite three steps and the third step is neither taught nor suggested by Onaivi. That is, Onaivi does not teach or suggest "selecting the test agent as a potential modulator of anxiety" based on binding to PKCε (claim 56) or on inhibition of PKCε (claim 64). The only other independent claim recites "administering . . . test agent [that inhibits PKCε] to an animal; and . . . measuring one or more indicators of anxiety to determine whether the test agent modulates anxiety in the animal." Thus, all three pending independent claims incorporate an element that is based on the Applicants' demonstration that reduced PKCε correlates with a reduction in anxiety *in vivo*.

The Examiner relies on a number of teachings of Onaivi, none of which teach or suggest the correlation discovered by Applicants, much less any of the methods recited in the pending claims. The Examiner notes that Onaivi "teaches effects of ibogaine treatment on cocaine abuse in ICR mice in [the] elevated maze test." *Id.* In particular, Onaivi teaches:

> Ibogaine did not by itself precipitate withdrawal anxiogenesis in the mouse model, but reversed the withdrawal aversions caused by cessation from cocaine administration. Therefore, it was concluded that ***if*** anxiety is a factor in drug dependency, then the antiaddictive property of ibogain *in vivo* ***may be associated with modifying the CNS neurotransmission that may be involved in anxiety***.

Onaivi *et al.*, page 241, second full paragraph (emphasis added). The Examiner has provided no line of reasoning as to how one skilled in the art would get from the highlighted speculation that ibogain

may modify CNS neurotransmission that ***may*** be involved in anxiety to the correlation of reduction in a particular PKC isozyme with reduced anxiety.

With respect to PKC isozymes, Onaivi teaches that "cocaine differentially affects the expression of the subtypes of protein kinase C"--Onaivi observed increases (*e.g.*, for PKCβ), decreases (*e.g.*, for PKCε), and increases or decreases, depending on dose (*e.g.*, PKCα). Onaivi, page 237. In addition, Onaivi reports an increase on total PKC activity in cocaine-treated PC-12 cells. Onaivi provides no basis for a scientifically credible conclusion that any of these effects are relevant to the *in vivo* effects of ibogaine, much less which, if any, of the PKC isozymes might be implicated.

The Examiner indicates that Onaivi teaches one skilled in the art that "a compound that alters PKC epsilon will have anxiety modulating activity as is the case with ibogaine." However, Applicants find no evidence in Onaivi for this conclusion and respectfully point out that what Onaivi says is, in fact, diametrically opposed to this statement. Onaivi concludes that it "***remains to be determined whether the signaling involving PKC is important in the antiaddictive properties of ibogaine***." Onaivi, abstract (emphasis added). This invitation to experiment with PKC isozymes generally is unquestionably not a teaching that PKCε plays a role in anxiety. The only document of record that could conceivably have led the Examiner to interpret Onaivi in this manner is Applicants' own specification. As the Examiner is no doubt aware, any reliance on Applicants' specification in interpreting the cited references is impermissible hindsight reconstruction.

Because nothing in Onaivi teaches or suggests that reduced PKCε correlates with a reduction in anxiety *in vivo*, nothing in Onaivi would lead one skilled in the art to select a "test agent as a potential modulator of anxiety" based on binding to PKCε (claim 56) or on inhibition of PKCε (claim 64). Similarly, Onaivi would not lead one skilled in the art to administer a"test agent [that inhibits PKCε] to an animal; and . . . [measure] one or more indicators of anxiety to determine whether the test agent modulates anxiety in the animal (claim 76). Thus, independent claims 56, 64, and 76 are clearly not anticipated by Onaivi. Claims 57-59, 65-68, and 70-80 depend, directly or indirectly, from one of these independent claims and are clearly patentable over Onaivi at least by virtue of this dependence. Withdrawal of the § 102 rejection over Onaivi is therefore respectfully requested.

Conclusion

In view of the foregoing, Applicants believe that all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (510) 769-3509.

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APPENDIX A

"MARKED UP" CLAIMS ILLUSTRATING THE AMENDMENTS MADE TO THE CLAIMS OF USSN 09/340,283 WITH ENTRY OF THIS AMENDMENT

56. (Amended) A method of screening for an agent that modulates anxiety, said method comprising:

a) exposing a PKCε to a test agent;

b) assaying for [detecting] binding of the test agent to the PKCε [, wherein the ability to bind PKCε indicates that the test agent is a potential modulator of anxiety]; and

c) if binding is detected, selecting the test agent as a potential modulator of anxiety.

57. The screening method of claim 56 wherein the PKCε is exposed to the test agent in vitro.

58. The screening method of claim 56 wherein the PKCε is exposed to the test agent by contacting a cell or cell lysate comprising the PKCε with the test agent.

59. The screening method of claim 56 wherein the PKCε is at least partially purified.

60-63. (Canceled)

64. (Amended) A method of screening for an agent that modulates anxiety, said method comprising:

a) exposing a functional PKCε, or a cell or cell lysate comprising a functional PKCε, to a test agent;

b) determining whether the test agent inhibits [modulates] PKCε [, wherein the ability modulate PKCε indicates that the test agent is a potential modulator of anxiety]; and

c) if the test agent inhibits PKCε, selecting the test agent as a potential modulator of anxiety.

65. The screening method of claim 64 wherein the exposing of (a) is carried out in vitro.

66. The screening method of claim 64 wherein the cell or cell lysate comprising the functional PKCε is exposed to the test agent.

67. The screening method of claim 64 wherein the functional PKCε is at least partially purified when exposed to the test agent.

68. (Amended) The screening method of claim 64 wherein determining whether the test agent inhibits [modulates] PKCε comprises measuring an activity of PKCε in the presence of the test agent.

69. (Canceled) The screening method of claim 64 wherein determining whether the test agent modulates PKCε comprises measuring the ability of the test agent to inhibit PKCε.

70. (Amended) The screening method of claim 64 [69] wherein determining whether the test agent inhibits [modulates] PKCε comprises measuring the ability of the test agent to selectively inhibit PKCε activity.

71. (Amended) The screening method of claim 64 additionally comprising:

c) administering to an animal a test agent that inhibits [modulates] the activity of PKCε; and

d) measuring one or more indicators of anxiety to determine whether the test agent modulates anxiety in the animal.

72. The screening method of claim 71 wherein the animal displays one or more symptoms of anxiety in the absence of the test agent.

73. The screening method of claim 71 wherein the animal is exposed to an anxiety-provoking stimulus prior to the measuring of (d).

74. The screening method of claim 71 wherein the measuring of (d) comprises measuring an indicator of anxiety to determine whether the test agent reduces anxiety in the animal.

75. The screening method of claim 71 wherein the one or more indicators of anxiety is/are selected from the group consisting of: time spent and distance traveled in the center of an open field, time spent and distance traveled on the open arms of an elevated plus maze, basal and stress-induced levels of stress hormones.

76. (Amended) A method of screening for an agent that modulates anxiety, said method comprising:

a) selecting an agent that inhibits [modulates] PKCε as a test agent;

b) administering the test agent to an animal; and

c) measuring one or more indicators of anxiety to determine whether the test agent modulates anxiety in the animal.

77. The screening method of claim 76 wherein the animal displays one or more symptoms of anxiety in the absence of the test agent.

78. The screening method of claim 76 wherein the animal is exposed to an anxiety-provoking stimulus prior to the measuring of (c).

79. The screening method of claim 76 wherein the measuring of (c) comprises measuring an indicator of anxiety to determine whether the test agent reduces anxiety in the animal.

80. The screening method of claim 76 wherein the one or more indicators of anxiety is/are selected from the group consisting of: time spent and distance traveled in the center of an open field, time spent and distance traveled on the open arms of an elevated plus maze, basal and stress-induced levels of stress hormones.